FOOD AND DRUG ADMINISTRATION

INTERNATIONAL CONFERENCE ON HARMONISATION PUBLIC MEETING: PREPARATION FOR ICH MEETINGS IN TOKYO, JAPAN, INCLUDING PROGRESS ON THE COMMON TECHNICAL DOCUMENT AND POSSIBILITIES FOR NEW TOPICS

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ASSOCIATED REPORTERS OF WASHINGTON
1523 North Carolina Avenue, N.E.
Washington, D.C. 20002
(202) 543-4809

FDA PANEL MEMBERS

JANET SHOWALTER, Chair
Office of International Programs

CHRISTELLE ANQUEZ
Office of International Programs

JOAN WILMARTH BLAIR, M.A.
International Affairs Advisor
Center for Biologics Evaluation and Research

JUSTINA A. MOLZON, M.S. PHARM., J.D.
Associate Director for International Affairs
Center for Drug Evaluation and Research

CHRISTY UNDERDONK
Office of International Programs

C O N T E N T S

P R O C E E D I N G S

(10:30 a.m.)

MS. SHQWALTER: Good morning, everyone, and welcome to the ICH public meeting. I am delighted to see so many people here today.

We have a number of handouts that are on the table right in front of the meeting room, and if you haven't already gotten a hold of those, you should do that because they are going to be important for what we are talking about at the meeting today.

The purpose of this meeting, for those of you who don't know -- and I imagine quite a few of you do -- we have an ICH meeting coming up in Tokyo, actually May 21st through the 24th. Some time ago, we made a commitment to transparency, and this was at the very beginning of the ICH process. That continues to be a very important component of the process. What we have tried to do is in recent time, prior to each ICH meeting, to have at least one public meeting where we can get input from you directly into that process because we think that this really enhances the transparency and communication of the process.

What we are going to be doing today -- you have a copy of the agenda. The meeting that we are about to have in Tokyo will primarily be focused on a single topic, and I do not think that topic is a surprise to anyone. We

are now in the process of implementing the Common Technical Document, which reached completion in San Diego in November of last year. Obviously, this has been a very busy and hectic time for FDA in terms of doing that. The meeting in Tokyo is going to focus primarily on what the three primary regions of ICH are doing with respect to that document.

Unfortunately, our ICH person from Canada had intended to be here today and was unable to be here. But they are also implementing the ICH Common Technical Document in Canada and have done a great deal of work in that area, so we will be hearing about that as well.

In addition, another observer country, Switzerland, is also in the process of implementing that document as well, and we will be hearing from them at the meeting in May.

The purpose of this meeting is to bring you up to date on the significant activities that we have had underway toward this goal of implementing the Common Technical Document. At least half of this meeting today will be focused on that particular topic, and you will hear from both of our centers, our Center for Drug Evaluation and Research and our Center for Biologics Evaluation and Research, about what they are doing in that regard.

Following that, we are going to turn to all of you because we also expect the subject of the future of ICH

to come at the meeting in Tokyo as well. I want to reiterate, I think when we last had a public meeting, we thought we would probably be a lot closer to determining the future of ICH than we are at this point in time. If you went to the meeting in San Diego, we put forward a very general thought piece at that meeting, and copies of it are outside of this room and available to you.

What we had hoped to do was to really focus that work at this meeting that is coming up in Tokyo. However, given the resource intensity that we have had to deal with in terms of implementing the Common Technical Document, we probably will not be as far along on discussing the future as we had originally intended. However, we do expect this topic to come up.

As you will recall, at our last meeting, we had discussed postmarketing surveillance as possibly one of the topics that we might want to turn to for future directions.

What I am also making available to you today is a copy of a document that has not been released before, but we did get permission from MHLW, our Japanese colleagues and partners in the regulatory area, to release that document. It is a document they put together discussing the various aspects of postmarketing surveillance that might be of interest to take up in ICH. I would just call your attention to the fact that that document is really

broken out into three primary sections, and that would be the area of risk communication, the area of roll-out of new drugs, and also the area of periodic safety update reports. These are some of the things that we will consider at the meeting in Tokyo, so you should take a look.

We will also be delighted today to have comments from anyone in the audience who would be interested in providing some input at this point in time, recognizing that there will be additional opportunities also for input.

So, this will be the second major phase of the meeting today.

Now, prior to getting started, with those two aspects of the program, what I would like to do is call on Christy Underdonk from the Office of the Commissioner, the Office of International Programs who will present sort of a refresher course for all of you on the rules and procedures of ICH. This will just be a quick overview.

MS. UNDERDONK: Good morning. ICH stands for the International Conference on Harmonisation for the Technical Requirements for the Registration of Pharmaceuticals for Human Use.

ICH is a joint initiative involving both regulators and industry from the European Union, Japan, and the U.S. as equal partners. ICH harmonization is achieved

through scientific and technical discussions and consensus on the testing procedures required to assess and ensure the safety, quality, and efficacy of medicines. ICH guidelines are developed to harmonize the technical requirements that must be met for regulatory submissions in the EU, Japan, and the United States.

ICH was created in Brussels in April 1990 at a meeting hosted by the European Federation of Pharmaceutical Industries Association. Representatives of the regulatory agencies and industry associations of Europe, Japan, and the U.S. met primarily to plan an international conference on harmonisation, and this name was then given to the initiative.

The meeting also discussed the wider implications in terms of reference of ICH, which ended in the creation of the ICH Steering Committee.

The objectives of ICH are the identification and elimination of the need to duplicate studies to meet different regulatory requirements, more efficient use of human, animal, and material resources in the R&D process as a consequence, and quicker access to patients of safe and effective new medicines.

Since the focus of ICH has been on the technical requirements for medicinal products containing new drugs and because the majority of those new drugs and

medicines are developed in western Europe, Japan, and the United States, when ICH was established, it was agreed that its scope would be confined to the registration in those three regions. Therefore, the founding members of ICH represent the regulatory bodies and research-based industry in the European Union, Japan, and the United States.

These parties include the European Commission and the EU, the European Federation of Pharmaceutical Industries Association, EFPIA, and in Japan, the Ministry of Health, Labor, and Welfare, and the Japanese Pharmaceutical Manufacturers Association, and in the U.S., the FDA and the Pharmaceutical Research and Manufacturers of America.

ICH is administered by the ICH Steering Committee, which is supported by the ICH Secretariat. Since ICH was established, each of the six cosponsors has had two seats on the ICH Steering Committee, which oversees the harmonization activities. Each of the six parties has an ICH coordinator. The IFPMA provides the Secretariat and participates as a nonvoting member of the Steering Committee. Scientific and technical discussions occur within the expert working groups.

The core of the ICH structure is the Steering Committee, with two representatives from each of the six parties, plus one nonvoting IFPMA representative. There

are also three nonvoting observers to the ICH committee. The observers are Health Canada, European Free Trade Association, and the World Health Organization.

Expert working groups are formed for each new topic. If one of the six parties feels that they have a suitable topic for harmonization, they prepare a proposal or a concept paper which outlines the subject, the need for harmonization, and the anticipated outcome. This paper goes forward for consideration at the next Steering Committee meeting where it will be discussed. If the Steering Committee accepts the proposal, then an expert working group is formed.

ICH has approved almost 40 guidelines aimed at removing redundancy and duplication in the development and review process. ICH is currently working on the implementation of the CTD to be used in reporting the technical requirements for a new products submission to regulatory authorities. These guidelines or guidances, according to FDA's good guidance practice, may be found on CDER's website.

On the basis of experience to date, the Steering Committee has outlined a step-wise ICH process for monitoring the progress of the harmonization work and identifying the action needed in order to reach a harmonized guideline.

At step 1, a six-party expert working group is appointed for the topic, and one of the topic leaders is designated as the rapporteur. Preliminary discussions on the topic are held between expert working group members, and a first draft is prepared by the rapporteur. The draft is reviewed and revised by the experts and successive drafts are prepared until a consensus is reached on the scientific issues. The draft is then forwarded by the expert working group to the Steering Committee.

At step 2, a draft is signed off by the six cosponsors in the Steering Committee and is transmitted to the three regional regulatory agencies for formal consultation in the EU, Japan, and the U.S. in accordance with their normal internal and/or external consultation procedures. This regulatory consultation may include organizations and associations outside the ICH process, as well as IFPMA, EFPIA, JPMA, and PhRMA, and the observers in Canada, EFTA, and WHO. The comment period should normally be six months, except when there are special circumstances to take into account.

At step 3, a regulatory rapporteur is designated from the EU, MHLW, or the FDA. Comments are collected by the regulatory agencies in the three regions and exchanged with the other regulatory bodies. The regulatory rapporteur, in consultation with the other

regulatory experts, analyzes the comments and revises the step 2 draft, if necessary. When significant changes result from the consultation process, such that the original consensus is not maintained, one or more regulatory authorities may recirculate the revised draft. In other cases, the regulatory rapporteur prepares the final draft and shares this with the regulatory experts from the other parties. The final draft is referred to the ICH expert working group and signed off by the experts designated by the regulatory parties before being referred to the ICH Steering Committee for adoption.

At step 4, the final draft is discussed within the Steering Committee and signed off by the three regulatory parties to ICH. It is then recommended for adoption to the three regulatory bodies.

And at step 5, the process is complete when the full recommendations are incorporated into domestic regulations or other appropriate administrative issues according to national or regional internal procedures.

Biennial International Conferences on Harmonisation have been important for disseminating information on ICH and for ensuring that harmonization is conducted in an open and transparent manner. Our first major conference was held in Brussels in 1991, and ICH 2 was held in Orlando, Florida in 1993; ICH 3 in Yokohama,

Japan in 1995; ICH 4 in Brussels in 1997. The fifth ICH conference was held in San Diego, California November 9 through 11, 2000, marking the 10th anniversary of ICH. The conference followed meetings of the ICH Steering Committee and expert working group meetings at which a final CTD was completed. At ICH 5, it was also announced that the sixth ICH conference would take place in Japan in the fall of 2003.

Thank you.

MS. SHOWALTER: Tanks, Christy. What we will do before you sit down -- if there are any clarifying questions, feel free to ask them at this time on the procedures and the rules. Otherwise, we will move into the main body on the agenda. Any questions?

(No response.)

MS. SHOWALTER: Thank you.

The next part of the program is the discussion of what has been happening at FDA with respect to the Common Technical Document. As I mentioned, one of the things that we think is really critical to the success of implementing this program is communication, and I think we have put in place some really good systems for that not just in the U.S., but also in Europe and Japan and Canada.

There have been a number of public meetings. There was a DIA public meeting. I do not know if any of

you attended that meeting in March of this year. There also have been public meetings in Europe and Japan and, in addition, Canada has had at least one public meeting that I am aware of.

So, I think that as we move forward, communication is going to be the key, not just within the ICH process, but also internally. We have done a lot of work in terms of rolling out the CTD internally and the two centers have met extensively to talk about progress and the way forward.

In addition to that, we will shortly have available a general considerations document that explains how to use the CTD when submitting to FDA using that format. I also understand that the CTD itself will publish very shortly in the Federal Register. It is on its way to publication even as we hold this meeting.

So, I will now turn it over to my colleague and the Steering Committee member for CDER, Justina Molzon.

MS. MOLZON: When I am commenting on the CTD, it would be really helpful if everyone had a copy of this triangle to refer to. I put this on the table outside. It makes it a little easier to understand.

Good morning, everyone. I am basically going to talk about implementation of the ICH CTD and let you know where we are in the process.

First of all, I really have to acknowledge the hard work of all the members on the four CTD working groups. That is safety, efficacy, quality, and regulatory communications. These people worked so hard all through the night on numerous occasions to get these documents completed.

So, as Christy mentioned, the fifth International Conference on Harmonisation took place in San Diego this past November, and it show-cased the CTD.

The Common Technical Document is basically organized into five modules. Module 1 is regional specific. Modules 2, 3, 4, and 5 are intended to be common for all the regions.

Module 1, as I have mentioned, has administrative information and prescribing information. This module should contain documents that are specific to each region, for example, our application forms, the proposed labeling for the region, and the content and format of this module is specifically relevant to the regulatory authority you are submitting the document to.

Module 2 contains Common Technical Document overviews and summaries. There was a lot of discussion about what to call these. So, there is an overview which isn't as involved as a summary which is more involved but still a summary.

So, module 2 should begin with a general introduction to the drug, and this includes the pharmacologic class, the mode of action, and proposed clinical use. As I have mentioned, module 2 also provides the quality overall summary. Quality has only an overall summary. It doesn't have an overview and a summary. And then the nonclinical overview and the clinical overview. Then module 2 also contains the nonclinical written summaries, the nonclinical tabulated summaries, and the clinical summaries. So, what you have are two layers: overviews and then summaries. That is explained in the triangle I provided.

Module 3 then contains information on quality topics.

Module 4 contains the nonclinical study reports.

And module 5 contains the clinical study reports.

So, this slide helps people that like a more visual approach, and this just mentions how everything fits together. But the handout that I provided provides much further information because based on comments we had at the DIA meeting, people couldn't figure out how all of these pieces interleaved. So, the triangle provides a numerical method of figuring that out. So, it helps in the assembly

of the documents. The Regulatory Affairs professionals at the DIA meeting said that the CTD document itself was confusing in how this all leafed together, so we tried to come up with something that was very exact in the presentation.

Much work has also been done on the electronic counterpart of the CTD or the eCTD. This gets confusing because you have the CTDe. Well, you also have the eCTD, which stands for the Electronic Common Technical Document. By necessity, this effort is six months behind the harmonized format. So, it is six months behind the documents from the November meeting. It is very difficult to describe specifications for an electronic transmission if you don't know what the document is, so they had to wait for the completion of the CTD in November.

Essentially the eCTD will be a transport format, which is intended to be moved into the agency's review environment and will facilitate electronic submissions.

Step 2 of the eCTD is targeted for the ICH meetings in Tokyo this month.

Now, each ICH region is in the process of developing an implementation plan for acceptance of the CTD. After the meetings in November, the regulators when back to their regions and worked on implementation issues.

We are working together with our fellow ICH regulators to help promote consistency across the various regions for further harmonization. We are striving for transparency and communication, and that helps industry gauge their CTD activities accordingly. And today's meeting is, once again, an effort in helping with these transparency efforts.

Now, at the ICH meetings held in San Diego, the ICH regulators -- that is Japan, the European Union, Canada, Switzerland, and the U.S. -- discussed implementation of the CTD. We met as a group. As a result of these discussions, we developed Regulatory Considerations for Implementation of the CTD, and we agreed to work together, once again, towards a harmonized, synchronized approach. We also identified topics and mechanism for discussion by regulators, and we promised to work with industry to establish implementation/monitoring task forces.

We also agreed on a target date for acceptance of the CTD, and that date is July 2001. Japan has said July 1, 2001. We have never committed to an actual date, and when pressed, I always say July 32nd.

(Laughter.)

MS. MOLZON: So, if things go as planned, a company that is wishing to submit an NDA in CTD format can

do so in July, but I must emphasize that this is purely on a voluntary basis. At some point we will discuss mandatory implementation of CTD, but that will not be for quite a while. It would not make sense to implement the paper version. I think we would be waiting until the electronic CTD has been established because, as you know, our guidances are purely that. Guidances are not mandatory. For us to make something mandatory, we have to go through formal rule changes and that takes quite a bit of effort. So, we want to make sure that we have a final product.

So, at the FDA, we are in the process of determining how the final CTD fits into our current regulatory scheme for submissions. We may need to make changes in our existing regulations to accommodate the CTD. We are looking through the regs to make sure there is no specific format wording, and if there is something that will impede implementation of the CTD, we are considering a general waiver. We haven't found anything yet, but as we have more discussions in May, something might just pop up. So, we have been working with groups consisting of the reviewers that worked on the CTD and also people from our regulatory policy staffs, the attorneys, to make sure that the CTD and the CFR mesh together.

Now, some of the questions we're in the process of addressing include: How do we incorporate our regional

specific information into the CTD? Is it just going to go into Mod 1, or will it be put into some annexes? How do we relate the CTD submission to the information we already require? And how to apply the CTD to other FDA submissions for consistency? And by other submissions, I mean generics, over-the-counter products, supplements, and possibly other categories.

We are planning on issuing a guidance for industry called the General Considerations for Submitting Marketing Applications According to the ICH/CTD Format. This will be issued in time for voluntary submission of the applications. So, that means it has to be finished and published before July, hopefully towards the beginning.

The guidance will discuss what we expect to be submitted and this is especially important in Module 1 where we have to clarify the regional specific items. The FDA is the only one addressing that particular section for Mod 1. We will provide a physical description of the submission, and we'll indicate the CTD requirements that need to be addressed. We will also list guidances that have been made obsolete by the adoption of the CTD, and we will describe the logistics of the submission. And time frames will also be discussed, and there will probably be a section in there talking about the possibility of making something mandatory or not.

So, to provide you with more specific information, since I cannot actually hand the guidance out, I am really just going to go through and talk about the major topics. One of the goals here is to demystify it. This is just a very straightforward guidance. It's actually pretty boring, if guidances can actually be exciting.

(Laughter.)

MS. MOLZON: Module 1 is thoroughly described within this guidance. It talks about the administrative information specific to FDA, and it includes FDA form 356h. That is the cover form that you are now using. We are just going to put that on top, a cover letter, patent information, debarment certification, field copy certification, user fee cover sheet, financial disclosure information, letters of authorization for reference to other applications or drug master files, patent certification, waiver requests, claimed exclusivity, labeling -- this is the package insert -- and then container and package labels, and annotated labeling. These are things everyone is submitting. We are just going to tell you it has to be in this order and it is on the top of the pile.

Now, in terms of general issues of submissions, we are going to talk about how this applies to amendments

and supplements, how the documents are organized. Once again, a large chunk of this guidance is looking at the Common Technical Document, and we are explaining how we want it interleaved together. That is why we came up with that triangle to make sure that there is no ambiguity on what section comes before another one.

The general issues section will also talk about the number of copies, and that's for archival, review, and field purposes. It will talk about the paper size. We have never harmonized in ICH on 8-and-a-half by 11 to whatever Europe uses. So, we have the requirement that it has to be on 8-and-a-half by 11.

The margins, the fonts, how the volumes will be bound, the colors of those volumes, the volume size. The goal here is to be able to share the overview and summary documents between disciplines, so we do not want those documents to be very thick. We want to be able to distribute these. How to identify the volumes, how to use pagination within the various volumes, the size of the packing carton, and then actually the address where to submit the information.

So, internally, we still have to address training and transparency issues. Before the ICH meetings in November, we had a large effort on roll-out of the CTD. We wanted to get everyone's input into the document before

we went to finalize it. So, we've actually started our training because all of the reviewers, the pharm/tox, the chemistry and the medical officers, all have been exposed to these documents. As we get closer to finalization, we will be setting up training programs. We will have this for industry for transparency issues. We are also going to have to train our document room staff because they are the ones who will be getting the new documents, and they need to know how to process them and how to distribute them.

We will map our current processes to the processes that are required by the CTD.

We will also create a feedback mechanism so industry can let us know if there are problems. We are still working out the details on this. This could be just merely a website address where people send in their comments. We might have an electronic docket established. There has to be a way for people with questions to get the questions to us so that we can deal with them.

I should mention in the implementation working groups that are meeting in Tokyo in the next couple of weeks, one of the responsibilities is to address frequently asked questions. We have a lot of questions from the ICH meeting that took place in San Diego. We have had questions since then. We are going to try and summarize those questions and address them in an FAQ pattern so when

the document is published, you can go to that section and see if you have any similar issues.

Finally, we will continually update everyone through meetings like this or meetings with DIA, or whatever. We will update everyone, industry as well as our fellow regulators, on our progress.

Thank you very much.

MS. SHOWALTER: Thank you, Justina. Thank you for being so comprehensive.

However, it is a lot of information to absorb in a relatively short period of time. So, if there is a need for clarifying questions, we should get those out of the way before we continue. Since we are making a transcript, if you could identify yourself and speak into the mike, that would be helpful.

DR. LEHMANN: Craig Lehmann, August Consulting, Austin, Texas.

A number of sponsors, of course, are having to implement mandatory Common Technical Document submissions in Europe, MAAs and that sort of thing. It would be helpful to know if there is an internal schedule within FDA that matches that. It sounds like it's going to take more time within FDA to implement some sort of a mandatory time for requiring the Common Technical Document. But is there an internal schedule that you can share with us within FDA

where that might be projected at this time?

MS. MOLZON: There is no internal schedule. ICH documents are guidances. Therefore, they're not mandatory. For us to make something mandatory, we have to go through formal rulemaking. We know that this will be after the Electronic Common Technical Document has been established, but we don't actually know when that would be. That would be the internal time table. We don't want to have this paper interim format mandatory. My analogy has been if you picture new cars that are being created in Detroit, they have a model. They start with clay and then build up to something that they can then put on the assembly line. We want to make sure that we have something final before we go about changing the CFR because that just takes so long. So, we want to make sure that we have all the information, and when we do it, we'll do it right the first time. So, there is not going to be an interim step.

Part of that is tied into CDER and CBER's efforts toward electronic submissions. We have to make sure that the eCTD matches with the electronic submission efforts. So, all this has to work together.

It's difficult to make something mandatory when you have to also pay attention to the needs of the industry. Some of the industry won't have the capability to do total electronic. So, these are the things we're

wrestling with. So, it's much more difficult for us as opposed to Japan or the European Union where they just publish something and say it's mandatory. Because of our good guidance practices and other issues, we can't do that.

Bob Yetter from CBER, did you want to add anything to that? Bob Yetter is the Director of Policy at the Center for Biologics.

MR. YETTER: Yes. As Justina has pointed out, to make something like this mandatory would require notice and comment rulemaking. Although we have done that on a shortened time frame in the past, a shortened time frame still is not quick. You don't want to go into notice and comment rulemaking and find yourself halfway through the process and realize that you forgot something or that you want to make a slight change. It makes life difficult. There are a lot of different pieces that have to be reconciled before you can actually go into that.

On the other side of that, just because it's not mandatory doesn't mean that you can't do it. This is voluntary. As of July 32nd, as you heard Justina say, you can go ahead and do this.

DR. LEHMANN: Thank you very much. That helps a lot. We're just trying to coordinate what's going on in Europe. Since sponsors are preparing a number of common submissions, it would be helpful to coordinate.

MS. MOLZON: Thank you. Any other questions?

MR. LUCEK: You said the electronic CTD was about six months behind the paper CTD. Can we expect some sort of guidance coming out or direction from the agency in January or February of the coming year 2002 with respect to the electronic submission?

And my other question is if you're preparing a CTD now which you're planning on submitting electronically, can you be guided by the documents already issued by the agency for the preparation of electronic NDAs but adapt them to the CTD to come up in an electronic CTD?

MS. MOLZON: The answer to the first question is at the end of the meetings in Tokyo this May, we are anticipating the Electronic Common Technical Document working group reaching step 2 in their document. So, in the ICH process, as Christy mentioned, step 2 is the first draft. So, that document will be published for comment. So, you'll have something, if the group goes as planned, at the end of May.

In the General Considerations document, there will be a section on just that, how to adapt the document to the electronic submission process, because this isn't going to be a total paper CTD. So, PDF formats will be allowed because we're already allowing that. So, we're trying to blend it. There will be a section in the General

Considerations document that explains that.

Anyone else?

MS. SHOWALTER: I'm sorry. For the record, could you identify yourself into the microphone for the transcript? Thank you.

MR. LUCEK: Rudy Lucek, Yamanouchi USA.

MS. SHOWALTER: Thank you. Any other questions for Justina?

MS. STINSON-FISHER: Carol Stinson-Fisher from AstraZeneca.

You mentioned in your presentation about working with industry to establish an implementation task force. Can you elaborate a bit more on what has been done for that or what will be done?

MS. MOLZON: At the November meeting, the expert working groups completed their work on the documents. The meeting in Tokyo in a couple of weeks will consist now of implementation working groups. So, we have people that were the technical experts on the expert working groups, and we're bringing new players to the meeting that have to deal, in FDA's case, with the logistics of submissions. So, we're trying to make sure that the thoughts that were in the original documents are carried through and then we adapt our process to these new documents. So, that means we're bringing people that are

super project managers that are used to dealing with the documents and the work flow to make sure that we can make this work together.

Then industry is an important part of this because industry does this for a living, they assemble the documents. So, we want to make sure that our interpretation flows well with their thoughts. So, that's where the implementation working groups are taking place in these next meetings.

I'm assuming that your company is a member of PhRMA. The PhRMA ICH Coordinator is Caroline Nutley Loew, and you can send her your questions or issues, and they could also be brought up at the meeting. Or if you have questions after the documents are published, we can try and answer them in this FAQ exercise we're talking about. So, industry and the regulators are working together now in implementation working groups.

But as I said in my talk, the regulators were given from November until March of this year to try and figure out how this all fit together, and we've shared that information with PhRMA in our case. Now we're at the next step. We're just trying to finalize this and make it work.

Anyone else?

(No response.)

MS. MOLZON: Like I said before, I'll still be

available for questions if you think of something else. Thank you.

MS. BLAIR: I just wanted to make a comment in follow-up to Justina's response to the question. PhRMA has offered to query its membership and find volunteers to generate a mock CTD that would be helpful for us to work with. So, if your company is interested in volunteering to generate a mock CTD, that would be helpful also. That would be part of the exercise of implementation to get a hands-on experience with a quasi-real document.

MS. SHOWALTER: Thank you and thank you, Justina.

I think it's worth taking a few minutes here to pause and reflect on some of the information that has been presented in terms of what you ought to be looking for.

First of all, as I understand it, while we are in Tokyo in May, the CTD final version will be published in the Federal Register, likely. So, that's about May 21st or so, if everything goes according to plan. That document is worth taking a look at. You may have looked at the document on the IFPMA website or otherwise. This version will be in GGP format, so some of the numbering and so forth has been changed to be consistent throughout. So, we encourage you to make sure that you take a look at that document.

The other thing, as Justina mentioned, that will be coming out from the agency -- and I think a question I have is where will this first appear -- is the General Considerations document. Is that going to be a Federal Register notice?

MS. MOLZON: No. It will just be posted on the Web.

MS. SHOWALTER: So, another thing to look for on the website is the General Considerations document which will give specific guidance on how to use the Common Technical Document.

And then another item to keep in mind, because I know we are getting a lot of questions about mandatory implementation dates. What I have understood the Europeans and the Japanese to say, in the past at least, is that they will not be moving toward mandatory submission of the CTD until the year 2002. So, if people have different information than that, I think that, of course, is something we would like to know.

Also, it's worth knowing, I think those of you here from industry, that your ICH Coordinator is in the audience. I'm sorry I did not notice that early on. Caroline Nutley Loew is here. You can hand your questions directly to her. Caroline, do you want to stand up so that they know who you are? Thank you and thank you for

attending.

In addition to that, one of the things that we will do, as we move forward and get additional questions and input, we do have a number of experts. Justina has already identified Bob Yetter. We have other people from the centers here as well. So, we may be referring some questions to them.

Having said all of that and the things that you ought to be on the lookout for -- yes?

MS. MOLZON: Well, I just wanted to mention that one of the reasons we were late in publishing the documents that came out of San Diego in November is that our editors put a lot of effort into taking these three different documents developed by different groups and turning them into three consistent documents in terms of style, format, good guidance practices, and the numbering. So, this is our effort in trying to make these documents more easily understood. So, we'd really appreciate people letting us know if we, in fact, helped the situation.

Our thoughts are to publish the General Considerations document as soon as we get back from Tokyo. We just want to make sure, once again, that we're not missing something. So, as Bob mentioned, it's much more difficult to start something and pull it back. The document is generally completed, but we just need to make

sure, by getting feedback from our fellow regulators, that we're in sync, that we're doing things the same. So, that document is paused for a moment but will be published as soon as we get back from Tokyo.

MS. SHOWALTER: And published means it will be available on the website.

MS. MOLZON: Yes.

MS. SHOWALTER: Now, moving on with the program today, we have Joan Blair, our colleague from the Center for Biologics, who will talk to us about CBER's perspective on the CTD.

MS. BLAIR: Good morning.

I'd like to spend a moment telling you who I am first in relationship to ICH, as you are all probably used to seeing Dr. Elaine Esber up here, CBER's ICH Steering Committee representative. Dr. Esber retired last month, and her seat on the Steering Committee will be filled by our Center Director, Dr. Kathryn Zoon.

My job title, as you can see, is International Affairs Advisor. I report directly to Dr. Zoon. In addition to my other international responsibilities, I will be providing the staff support to Dr. Zoon and the center in its involvement in ICH.

Let me start my presentation with the now familiar and quite lengthy descriptor for this initiative,

the International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use.

I am sure I'm covering familiar ground, but it's useful to refresh our understanding of what the term "pharmaceuticals" refers to as we think about the implementation of the CTD in the world of CBER. Here we have the oft-used CBER rainbow depicting the array of products that fall within our regulatory purview. Most of these product categories do not, in fact, fall within the scope of ICH.

I'd like to turn to the language in the ICH Guidance Q6B, Specifications for Biotech/Biological Products, to remind us of just what that scope is. Proteins and polypeptides, their derivatives, and products of which they are components, e.g., conjugates. Not covered are antibiotics, synthetic peptides and polypeptides, heparins, vitamins, cell metabolites, DNA products, allergenic extracts, conventional vaccines, cells, whole blood, and cellular blood components.

So, back to the rainbow. We can see that in the world of CBER, ICH addresses only one subset of the full range of CBER products.

The reasonable question then is, will the CTD application format only be applicable to BLAs for this

subset of products? I'd like to pause and point out an important concept that is inherent in my phrasing of this question. Let me repeat the question. Will the CTD application format be applicable to BLAs?

We all need to remember that the CTD refers to an application format. It does not refer to the application type. That is, the BLA does not disappear with the adoption of the CTD format.

The application for the licensing of a biological product is the biologics license application, the BLA, as we all know. Its content and procedures for filing it are described in section 601.2 of the Code of Federal Regulations. Similarly for drugs, the NDA is described, albeit in much greater detail, including formatting of submissions, in section 314.50 of the CFR. These application types exist by virtue of regulation.

The CTD, on the other hand, is a formatting of the requirements of these licensing applications. So, the question is not will CBER be accepting the CTD instead of the BLA, but rather will the CTD application format be applicable to all BLAs.

The first point to be made in answering this question is that the regulations describing the BLA do not address format, as do those for the NDA. Our review of the BLA regulations conclude that there are no regulatory

impediments to effect the adoption of the CTD format; that is, no changes would be needed to the regulations. Additionally, this means then that an applicant could use the CTD format for the BLA for any given product as long as all the content requirements were met. Again, the regulations speak to content not format.

A second consideration is the guidance for the implementation of the CTD. It is useful to consider as a backdrop the relatively recent changes that were instituted with regard to the licensing of biologicals. In 1996, CBER undertook the migration from a dual licensing model -- that is, the establishment license and the product license -- to a single licensing model, the BLA. At the same time, CBER and CDER undertook the harmonization of their application formats, culminating in the adoption of the harmonized form 356h. This changeover required certain changes to be made to our regulations, followed by the issuance of a set of guidances that address the content and format of the new BLA tailored to CBER's different product categories.

Here we have the itemization of the guidances that were written addressing the content issues of the new license, as well as format issues. To effect a changeover to a CTD format, there will be a need to revise these so-called CMC guidances. A working group, led by Dr. Christopher Joneckis, has already begun revision of the

first of these guidances, that addressing specified products, essentially those biotech/biological products that have been addressed in the ICH process.

Of course, the question then becomes, will CBER accept the CTD format for the non-ICH products prior to issuance of a guidance? The use of the CTD will not be precluded in advance of the guidance inasmuch as the BLA regulations do not address format. However, we strongly urge any applicant to communicate with the center in advance of a CTD submission to assure that all required content is included.

In addition to the revision of guidances, it is clear, as has been said, that the integration of the CTD into the BLA will necessitate internal preparation on our part, which will, of course, mean staff training. We'll also demand outreach efforts to sponsors and manufacturers perhaps in the form of public workshops and stakeholders meetings, as was done during the changeover from the ELA/PLA to the BLA.

So, the take-home message is that the integration of the CTD into the BLA will necessarily unfold over a period of time, as revisions to guidances that map the old BLA format to the CTD are completed. We must all keep the lines of communication open, that outreach on our part is a necessity, that feedback on problems and concerns

on your part would be a constructive contribution to the process.

Thank you.

MS. SHOWALTER: Thank you, Joan.

Are there questions for Joan?

(No response.)

MS. SHOWALTER: There will be an opportunity later for questions as well if other things do come to mind.

Our next speaker will be Christelle Anquez, and she will talk to you about what's going on in terms of implementation in the other ICH regions. Christelle?

MS. ANQUEZ: Good morning, everyone.

You've heard about the implementation of the CTD in the U.S. I will now present the implementation status of the CTD in the other ICH regions, Europe, Japan, and one of the observers, Canada.

As you know, the ICH CTD guidelines were signed as a final document in San Diego at the last ICH meeting. Back home, the regulators of each region started drafting their CTD implementation document. In Europe this document is called Presentation and Content of the Dossier CTD. In Japan, it's Notification on General Principle of CTD Implementation. In Canada, it's called Preparation of Drug Submissions in the CTD Format. All three drafts have been

posted or published in April, and the comments are expected for early/mid-May.

The names of these documents are different. However, the content is really similar between the three regions. The documents lay out first the scope, the time frame of implementation. I will detail these two first items in the next slides. It also lays out the content of Module 1, the relationship between the previous format, and the CTD format, and the regulatory requirements.

Which products will be covered by the CTD format? In Europe, the CTD is intended to be applicable to all categories of medicinal products. In Japan, it will cover new chemical entities and new biologics, new indication, new route of administration, new dosage forms and dose. In Canada, it will cover the new drug submissions which are new chemical entities or biotech products. Then it will be extended to abbreviated new drug submissions and supplemental applications.

In San Diego, the time frame was agreed between the members, and all three regions agreed on a target date for voluntary submission, which is July 2001. And it will be made mandatory in Europe, and they decided that July 2002 will be the date. However, they said that they will be very flexible with that. Japan set up July 2003 as a mandatory date, and Canada has not yet decided a date to

set up the CTD to be mandatory. However, they work with the assumption of July 2002 for new chemical entities and biotech.

Another important feature of the CTD implementation process is the communication and sharing of information. In fact, in the past six months, we had telecons on a regular basis with the other regulators and sharing of information with the public and industry. Europe had a DIA workshop on the CTD in Paris in April, and some information posted as well on the European Commission website. Japan held an open forum with the industry in February, and Canada had two meetings with the industry in January, one in Montreal and one in Ottawa, a workshop with the stakeholders in April. And the CTD implementation is posted on the Health Canada website with the opportunity for the public to ask questions.

The implementation is going smoothly in the three regions. However, there are still questions, issues, things to be determined. In Europe, where to place the drug master file, the environmental assessment, the TSE provisions. What about the region-specific requirements? How to handle cross-referencing between the old dossier and the new CTD format. In Japan, where to place Module 5 and the list of patients. In Canada, placement of environmental assessment of new substances, cross-

referencing.

Finally, the training is one of the key factors of a successful implementation of the CTD. Europe will have three assessor training sessions, one each for quality, safety, efficacy in June-July in London. Japan organizes training sessions with industry in June in Tokyo and Osaka, and Canada is planning to have a joint industry/reviewer training but no date has been yet fixed.

As a conclusion and to summarize, I'll just say that the three regions are on track and that the first voluntary target date of July 2001 will be met. Thank you.

Any questions?

(No response.)

MS. SHOWALTER: Thank you, Christelle.

There are a couple of things that I think are worth highlighting in all of this as we close out the CTD before we see if there is any additional public input. First of all, we knew this was going to be a lot of work when we started the process, and we knew that the bulk of the work was really going to be in the implementation of the document. I think it's fair to say we have not been surprised. As you see, a lot has already been done, and we're doing I think one of the best jobs that we've done within the ICH process in terms of synchronizing the work in all the regions that are going to implement the CTD,

which of course is the goal, to maximize the usefulness of the document. I think, as you've heard today, that's on track and going well, but there remains a lot to be done.

The additional things to keep in mind and to keep on your radar screen are some of the training sessions that are going to be held. One of the things that I think we're going to make a more concerted effort to do is to collaborate together the ICH partners on the training so that we are implementing the CTD in the same way in all of the regions, to the extent possible, recognizing that in every case there's going to be the need for some additional information to be submitted, and the CTD does allow for that under the existing format.

However, I think that's something to keep in mind and we will also, as we train our reviewers internally, collaborate with our regulatory partners on this activity. Hopefully, that will continue to demystify and assist us in implementing the document.

What I'd like to do now is see if there are any additional questions or input from any of you in the audience. I also understand that Paul Gisby has requested to speak. I do not know if he is with us today. Yes. Did you want to talk on the subject of the CTD?

MR. GISBY: Yes.

MS. SHOWALTER: Then we'd like to hear from you

at this point in time. Thank you.

MR. GISBY: Thank you for the opportunity to speak this morning. I'm Paul Gisby from AstraZeneca. We just wanted to make some important points that we think would be useful to consider during the implementation phase.

AstraZeneca is a very keen supporter of CTD right from the beginning, but we do have a number of points that we think, as I said, are worth bearing in mind during this very important phase. These are represented by the bullets I have on my slide.

The first one, commitment, CTD, the future for us all. We thought long and hard about how to phrase this actually. I think the key word there is "commitment." Certainly the ICH initiative around CTD has talked in terms of CTD being the format for future submissions. But since the meeting in November last year in San Diego, there have been a lot of discussions and debates, and in some of those debates, there have been some suggestions that maybe CTD would assume the level of an alternative format rather than the main and single format. I think we would just like to say that we believe very strongly that that's not the correct way, that we should be adopting globally the one single format. We should be driving in that direction.

In connection to that point, I think we would

also want to ask that careful thought is given when considering regional supplements to CTD and supplementary information. We fully recognize that because of the way that applications are reviewed in different regions, there will be region-specific requirements and there will be region-specific supplements, if you like, and I suppose possibly the most famous of those so far is the integrated summary of safety which we know FDA have always said is outside of the scope of CTD.

But I think what we would want to say is please, when we're considering these regional requirements, can we try and make sure that we do restrict ourselves to issues that cannot be covered by CTD and don't add back region-specific requirements just because it appears to make the process within whatever authority more straightforward? Let's restrict ourselves to those things that can't be covered by CTD because if we don't do that, then there is a risk that we could end up reintroducing some of the repetition and redundancy which CTD is seeking to remove.

The second point, this thing about mandatory implementation, which there is a lot of discussion about I know. I suppose that what we really would ask for there is if we are going to harmonize our applications, then there seems to be a lot of sense in harmonizing any mandatory

introductory date. The draft notice to applicants that has been issued in Europe, upon which we have commented with others, is quite clear about making July 1, 2002 the mandatory date for implementation in Europe. This is only a draft I know, and that is still under consideration. But also MHLW in Japan has, as we've heard already, said that they're going to make their date 2003. Now, as we've heard again this morning, the situation in the U.S. with FDA is a little different. But I think it's acknowledged that there will be a point where it doesn't actually become strictly mandatory. There will be a point where the advice is very strongly from FDA that we should use CTD.

And it would seem to be much more sensible to harmonize that date right across all three regions, and certainly in terms of the global impact that CTD could have and in terms of getting acceptance, there seems to be a lot to be said for harmonizing on one date. So, we would urge certainly in Tokyo that those discussions are held and that we try and harmonize.

The third point, mixed dossiers. Within AstraZeneca, as I know is the case in many other companies I've spoken to, there is a drive towards starting to use CTD as soon as possible, but the reality of drug development and the reality of dossier building is such that these days we tend to start putting together our

dossiers a long time in advance of our submission dates. I know that several companies, us included, have got submissions that we intend to make which will be past any proposed mandatory date, if that should fall next year, where we have started to write some of this documentation already in an existing format. I think it would help implementation with industry if there was a degree of flexibility, at least during a transition phase, around the acceptance of information in mixed formats.

Now, what I mean by this is I don't mean mixtures within modules. I think we agree that that would be unacceptable, but for example, some of our quality data has already been prepared in a format that currently exists. Yet, our clinical data may well be prepared in the CTD format. During the transition period, it would help us and industry in general if we were allowed by negotiation to submit some modules in old format and some modules in new format.

Europe in their notice to applicants and again in a draft notice to applicants has been quite clear about this and has said, no, they don't think they'll accept mixed formats. Japan in their MHLW draft guidance has also been quite clear about not accepting mixed formats. And we've commented back to both of these groups to say, please can they reconsider that, and we would ask the same here of

this forum.

Finally, it's not directly related to the meeting and the discussions that will take place in Tokyo later this month, but we would like to just post a point about electronic standards. eCTD is something that is strongly welcomed. I know that it's welcomed within industry as a way of preparing dossiers.

But I think one clarion cry we'd like to make is in thinking about global electronic standards -- and I'm thinking here not just within the scope of eCTD but every single aspect of the preparation of documents in electronic form -- please let's have one single set of standards for documents and for file formats, et cetera. A very clear reason for that is that if we don't have that and if we do end up with differing formats and differing electronic standards, then there is a very real danger that we could actually undo and cancel out a lot of the savings that we've made in terms of efficiency and savings of time and cost that have been handed to us by CTD.

Thank you very much.

MS. SHOWALTER: Thank you for those comments. Will you be leaving that overhead with us?

MR. GISBY: Yes.

MS. SHOWALTER: Thank you. I think those were very reasonable comments, and we will take those with us as

we move forward with the process in Tokyo.

What I'd like to do is see if there is any other public comment at this point in time before we move to the remainder of the program today, or other questions as well. This is your opportunity to influence the process.

(No response.)

MS. SHOWALTER: If not, the next part of the program, as I mentioned in the introduction -- I'm not going to spend a lot of time on this today because I think this will come up only in a very preliminary way at the meeting in Tokyo. However, I think it's important to have the information together that we distributed.

What you should take a look at is the MHLW concept paper on postmarketing surveillance activities. This is segmented into three categories having to do with postmarket surveillance, and they would be risk communication, the early roll-out of new drugs, and also periodic safety update reports. I think these are the primary areas that we'll focus our attention on. Of course, as we get away from the periodic safety update report, this is an area that we have had some familiarity with in ICH and something that would be fairly concrete I think to try to tackle. The other two topics would be fairly innovative within the ICH process, and I think we

would need to take a close look at what kinds of adjustments we might need to make to that process were we to take those on.

However, I do want to reiterate this will be a very preliminary discussion, and it will be more food for thought than anything else. We will not be expecting to make final decisions on postmarketing surveillance topics at the meeting in Tokyo. So, we should have yet another opportunity to perhaps distribute to you prior to the meeting in Europe in the fall some more concrete proposals in these areas.

The other document that you have that deals with the future of the ICH process is the paper that was distributed at the meeting in San Diego on the future, which is a fairly general thought piece on where we might go with this program and how we might direct our activities. Again, you'll notice that postmarketing surveillance is mentioned in that paper as well as an area where we would probably put some of our focus for the future.

Are there any comments on those papers or anything relating to the future of ICH for the discussion meeting in Tokyo? I'd like to take this time for public input into that if there is any.

(No response.)

MS. SHOWALTER: If not, I think what we could do is offer a final opportunity for questions, should there be any, and any other comments from the panel today as well on things that we've covered.

(No response.)

MS. SHOWALTER: And if not, with that, I think we can close and adjourn the meeting today. I'd like to thank all of you for attending and thanks to our panel for speaking here today. It's a busy time for us getting ready for the meeting in Tokyo. Thank you.

MS. MOLZON: Also, thank you to the Advisors and Consultants Staff for setting the room up and taking care of us. Thank you.

MS. SHOWALTER: Thank you. The meeting is adjourned.

(Whereupon, at 11:43 a.m., the meeting was adjourned.)